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Major Parasitic Zoonoses Associated with Dogs and Cats in Europe

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Summary

Some of the most important zoonotic infectious diseases are associated with parasites transmitted from companion animals to man. This review describes the main parasitic zoonoses in Europe related to dogs and cats, with particular emphasis on their current epidemiology. Toxoplasmosis, leishmaniosis, giardiosis, echinococcosis, dirofilariosis and toxocariosis are described from the animal, as well as from the human host perspectives, with an emphasis on parasite life cycle, transmission, pathogenicity, prevention and identification of knowledge gaps. In addition, priorities for research and intervention in order to decrease the risks and burden of these diseases are presented. Preventing zoonotic parasitic infections requires an integrated multidisciplinary 'One Health' approach involving collaboration between veterinary and medical scientists, policy makers and public health officials.

Keywords: companion animal; Europe; parasite; zoonotic disease

Contents

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Introduction

Parasites are responsible for some of the most important and well recognized zoonotic infectious diseases transmitted from companion animals to man globally. The CALLISTO (**C**ompanion **A**nimal multisectoria**L** interprofessiona**L** and interdisciplinary **S**trategic **T**hink tank **O**n zoonoses) project, an EU Framework 7-funded project, was established to discuss and investigate infectious diseases transmitted between companion animals, man and food producing animals, aiming to focus on these diseases in Europe. Expert Advisory Group (EAG) V in the CALLISTO project discussed the most important parasitic zoonoses in Europe, describing their epidemiology and identifying priorities for research and intervention to decrease the burden of these infections. This review by the members of EAG V includes descriptions of the parasitic diseases considered as most relevant for CALLISTO, with further insights into their epidemiology, diagnosis and prevention, with identification of gaps in knowledge of these infections and recommendations for further research.

Toxoplasmosis

Aetiology

Toxoplasma gondii is a tissue cyst-forming coccidium (Protozoa, Apicomplexa) with a complex life cycle. The asexual phase of *T. gondii* development takes place in various tissues of herbivorous or omnivorous intermediate hosts and is linked to a sexual phase of development in the intestine of felids, the definitive hosts. There are three infectious stages in the life cycle of the parasite: tachyzoites, bradyzoites contained in tissue cysts and sporozoites contained in sporulated oocysts. The parasite can invade the gut, become systemic and localize in vital organs such as muscle and the nervous system. In most cases infection is subclinical, but devastating disease can occur (Cenci-Goga *et al.*, 2011). The virulence of *T. gondii* strains is highly variable and dependent on the genotype of the

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parasite. Many atypical genotypes exist besides the 'commonest' genotypes (genotypes I, II and III) first described from Europe and the USA (Shwab *et al.*, 2014).

Hosts and Life Cycle

Felids are the definitive hosts for *T. gondii*, but all warm-blooded vertebrates including man may serve as intermediate hosts and potentially be infected by bradyzoites in meat, by sporulated oocysts or by intrauterine tachyzoites (Dabritz and Conrad, 2010; Elmore *et al.*, 2010). *T. gondii* has become adapted to exploit multiple routes of transmission through a sexual cycle in the definitive host and asexually, through carnivorous behaviour and by vertical transmission. These different routes may operate synergistically to enhance transmission, but they might also provide a vehicle for selection leading to partitioning of strains in the environment. Human infections are acquired from eating undercooked or raw meat, such as pork and lamb. However, the prevalence of *T. gondii* infection in human populations that do not consume meat or eat it well-cooked, suggests that the acquisition of infection from the environment, via oocysts in soil, water or on uncooked vegetables, may also play an important role in transmission. Only a small proportion (<0.1%) of infected people acquire infection congenitally (Lindsay and Dubey, 2011).

Epidemiology

Latent infections with *T. gondii* are common in domestic cats throughout the world. Antibodies to *T. gondii* may be detected in up to 74% of adult cats, depending on the type of feeding and whether cats are kept indoors or outdoors (Tenter *et al.*, 2000). After primary infection, cats spread *Toxoplasma* oocysts in their faeces within 3–10 days and shedding continues for approximately 7–21 days (median 8 days), with up to hundreds of millions of oocysts shed in the faeces of a single infected cat (Dubey, 2001). Afterwards, the direct risk for cat owners is limited.

T. gondii infects up to a third of the human population of the world. In Europe, European Commission (EC) Directive 2003/99 stipulates that member countries report human seroprevalence results every year or every other year, according to their epidemiological status (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:325:0031:0040:EN:PDF). Despite this directive, accurate information is incomplete and the EC has applied to the European Food Safety Authority (EFSA) for recommendations on surveillance and control methods for toxoplasmosis for man, animals and food.

Diagnosis of Infection in Man and Animals

A diagnosis of infection by *T. gondii* can be established by the isolation of the parasite from various tissues, detection of specific DNA by polymerase chain reaction (PCR) or by carrying out serological tests. Currently, routine diagnosis of toxoplasmosis relies mainly on the use of serological assays that are available for both man and animals such as the Sabin–Feldman dye test, indirect fluorescent antibody test (IFAT), enzyme-linked immunosorbent assay (ELISA) or various agglutination tests. Most clinical laboratories use an ELISA for the routine screening of specific immunoglobulin (Ig) G and IgM, while other techniques are mostly reserved for reference laboratories (Robert-Gangneux and Dardé, 2012).

Isolation of the parasite by mouse bioassay is a laborious and time-consuming technique, and represents the 'gold standard' for the detection of *T. gondii* in meat for human consumption (Villena *et al.*, 2012). It is still used for diagnosis in people with immunosuppression (Robert-Gangneux and Dardé, 2012).

Over the past two decades, PCR-based tests have been developed to detect parasite DNA in human and animal tissues. Nevertheless, this molecular diagnosis remains unsatisfactory due to a low sensitivity compared with the mouse bioassay, lack of standardization and a considerable diversity among DNA extraction methods, amplification systems and DNA primers (Sterkers *et al.*, 2010). In an attempt to increase the sensitivity of detection, a method based on sequence-specific magnetic capture of *T. gondii* DNA followed by DNA amplification has been developed (Opsteegh *et al.*, 2010).

Prevention of Infection in Man and Animals

Control measures should be aimed at the prevention of oocyst shedding in order to reduce infection of people with *T. gondii* (Tenter *et al.*, 2000). The risk for exposure to *T. gondii* parasites is greatest in cats that prey on wildlife and live outdoors or in farms. Kittens are very susceptible to infection and shed greater quantities of oocysts. Efforts to develop a *T. gondii* vaccine for cats should be renewed, which will lead to better protection of people (Robert-Gangneux and Dardé, 2012). Responsible cat ownership should also be encouraged. This includes measures such as collecting faeces in litter trays for ultimate disposal

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in rubbish destined for landfills, which are designed to prevent waste materials leaking into groundwater. In addition, cat faeces should not be disposed of in toilets.

Human infection can be acquired either by ingestion of infected raw or undercooked meat or by ingestion of sporulated oocysts from the contaminated environment. As a consequence, it is highly recommended (especially for high-risk individuals, e.g. previously unexposed pregnant women) that meat is consumed only after thorough cooking or freezing and personal hygiene in handling meat is mandatory. The control of human toxoplasmosis also relies on the avoidance of direct or indirect exposure to cat faeces. Proper faecal handling, litter tray management, removal of faeces from public areas and yards and hand hygiene are critical. Litter trays should be thoroughly cleaned every day so that any potential oocysts do not have time to sporulate (i.e. in about 48 h) (Dubey *et al.*, 2011). People, particularly those vulnerable to infection, such as pregnant women and the immunosuppressed, should avoid this task. Similarly, drinking unfiltered surface water or accidental ingestion of soil must be avoided.

Gaps in Knowledge and Recommendations for Further Research

A major gap in knowledge is the relationship between seropositivity in the main livestock species and presence of *T. gondii* in meat. There is a straightforward relationship between the level of antibodies detected in serum and the likelihood of isolating a viable parasite in pigs and sheep, but this relationship appears not to be clear for horses and cattle (Opsteegh *et al.*, 2011) and needs further investigation.

Another gap resides in the identification of the different sources of infection in various human populations. While multicentre studies pointed out the consumption of undercooked lamb, beef or game, contact with soil and travel outside Europe and North America as strong risk factors for acquiring infection with *T. gondii*, little is known about the relative importance of transmissions via tissue cysts versus oocysts in a given human population (Cook *et al.*, 2000; Jones *et al.*, 2009). The discovery of a sporozoite-specific protein, which elicited differential antibody production in experimentally infected pigs and mice, may contribute to filling this gap in knowledge (Hill *et al.*, 2011).

Further studies need to be undertaken in the field of molecular biology for standardization of PCR methods to be applied both in man and animals, while improvements need to be made in the sensitivity of these techniques for detecting viable parasites. Concerning the definitive host, there is need for advancement in the field of vaccination, with the objective of significantly reducing oocyst excretion, since felids represent the major source of environmental contamination.

Leishmaniosis

Aetiology

Leishmaniosis (or leishmaniasis) is a complex of mammalian diseases caused by diphasic protozoans of the genus *Leishmania* (Kinetoplasta, Trypanosomatidae). The *Leishmania* species endemic in Europe is *Leishmania infantum* and its most common zymodeme is MON-1. However, other zymodemes are also found in Europe. In addition, it is important to highlight that because multilocus enzyme electrophoresis, the classical reference method for *Leishmania* typing (Rioux *et al.*, 1990), is laborious and expensive, molecular typing methods of *L. infantum* isolates have been developed such as multilocus microsatellite typing (Gouzelou *et al.*, 2013) or multilocus sequence analysis, PCR with restriction fragment length polymorphism (RFLP) and whole genome sequencing.

Hosts and Life Cycle

The leishmanioses affect man and domestic and wild animals worldwide. Most transmission cycles are zoonotic, involving reservoir hosts such as rodents, marsupials, edentates, monkeys, domestic dogs and wild canids. Only a few *Leishmania* species are strictly anthroponotic (i.e. transmitted directly from person to person via sand flies) (Quinnell and Courtenay, 2009). Dogs are the major reservoir for canine and human *L. infantum* infection, in an area that stretches from Portugal to China and across South, Central and parts of North America, with the exception of Oceania. In Europe, the domestic dog is the only reservoir host of major veterinary and human importance (Solano-Gallego *et al.*, 2009). Infection in cats (Martin-Sanchez *et al.*, 2007), wild canids (Sobrino *et al.*, 2008; Millan *et al.*, 2011) and horses (Fernandez-Bellon *et al.*, 2006) has also been reported in areas where disease is common in dogs, but the role of these species as reservoirs remains unclear.

Natural transmission of *L. infantum* between animals and from animals to man occurs usually by the bite of a phlebotomine sand fly species (Diptera, Psychodidae, Phlebotominae) of the genera *Phlebotomus* (Old World) and *Lutzomyia* (New World). Sand flies are the only arthropod vectors that are adapted for the transmission of *Leishmania* species. *Leishmania* completes its life cycle in the sand fly, which harbours the flagellated extracellular promastigote form and in a mammal where the intracellular amastigote form

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develops. A female sand fly ingests *Leishmania* while blood feeding and then transmits the infective stages (metacyclic promastigotes) during a subsequent blood meal. The infective promastigotes inoculated by the sand fly are phagocytosed in the mammalian host by macrophages and other phagocytic cells, in which they transform to amastigotes.

Non-sand fly modes of transmission have also been described, but their role in the natural history and epidemiology of *L. infantum* infection remains unclear. Proven modes of non-sand fly transmission in dogs include infection through transfused blood products (Owens *et al.*, 2011) from blood donors that are carriers of infection (de Freitas *et al.*, 2006; Tabar *et al.*, 2008), vertical (Rosypal *et al.*, 2005; Pangrazio *et al.*, 2009; Boggiatto *et al.*, 2011) and venereal transmission (Silva *et al.*, 2009).

Epidemiology

Based on seroprevalence studies from Spain, France, Italy and Portugal, it has been estimated that 2.5 million dogs in these countries are infected with *L. infantum* and infection is spreading north in Europe, reaching the foothills of the Alps (Maroli *et al.*, 2008), Pyrenees (Chamaille *et al.*, 2010) and northwestern Spain (Amusategui *et al.*, 2004). The numbers of dogs travelling to southern Europe or imported as companion animals from areas where canine leishmaniosis is endemic have increased, as have the numbers of clinical cases reported in non-endemic countries such as the UK (Shaw *et al.*, 2009) and Germany (Menn *et al.*, 2010).

The seroprevalence in dogs in the Mediterranean basin ranges from 5% to 30% depending on the region (Solano-Gallego *et al.*, 2009). Surveys employing other detection methods to estimate the prevalence of *Leishmania* infection by amplification of *Leishmania* DNA from different tissues or by detection of specific anti-*Leishmania* cellular immunity have revealed even higher infection rates, approaching 70% in some foci. Most dogs in these areas appear to have chronic infection that may be lifelong, but only a small proportion of dogs develop severe disease (Baneth *et al.*, 2008).

In cats, serological and PCR surveys in southern Europe indicate that *Leishmania* infection is more widespread than clinical disease. Epidemiological studies have described rates ranging from 0.4% to 30% based on serological and molecular techniques (Martin-Sanchez *et al.*, 2007; Solano-Gallego *et al.*, 2007; Maia *et al.*, 2008; Millan *et al.*, 2011; Sherry *et al.*, 2011).

Human leishmaniosis, caused by several species of *Leishmania*, comprises a heterogeneous group of diseases. These include visceral leishmaniosis (VL), which involves internal organs and is fatal if untreated, and the cutaneous (CL) and mucocutaneous forms, which affect the skin or mucocutaneous junctions and may heal spontaneously, leaving disfiguring scars (Murray *et al.*, 2005). This group of infections is the third most important vector-borne disease after malaria and lymphatic filariosis. It is endemic in many tropical and subtropical regions of the Old and New World. Leishmaniosis is endemic in 88 countries, with more than 350 million people at risk. The estimated incidence is 2 million new cases per year: 0.5 million VL and 1.5 million CL cases (Desjeux, 2004).

There are only two transmission cycles with proven long-term endemicity in Europe: (1) visceral, cutaneous and mucocutaneous human leishmaniosis caused by *L. infantum* throughout the Mediterranean region and (2) anthroponotic cutaneous human leishmaniosis caused by *L. tropica*, which occurs sporadically in Greece. In Europe, about 1,000 people are estimated to be affected by clinical disease due to *L. infantum* annually (Dujardin *et al.*, 2008), although asymptomatic or subclinical infections are more frequent (Michel *et al.*, 2011). The high prevalence (2–40%) of asymptomatic human carriers of *L. infantum* in some areas of southern Europe suggests that this parasite is a latent public health threat. Asymptomatic infections are estimated to have a prevalence ratio of >100 asymptomatic:1 clinical case (Michel *et al.*, 2011).

Mediterranean VL primarily affects children as well as an increasing number of immunocompromised and immunosuppressed adult individuals, such as people who are positive for the human immunodeficiency virus (HIV) and people under immunosuppressive therapy. Mortality rates due to leishmaniosis in *Leishmania*–HIV co-infected patients can reach over 56% (Lopez-Velez *et al.*, 1998; Pasquau *et al.*, 2005). Therefore, risk factors for human infection include age, poor socioeconomic conditions, malnutrition and immunosuppressive conditions (Alvar *et al.*, 2006).

Diagnosis of Infection in Man and Animals

The most common techniques used for disease detection in man and animals include microscopical observation (i.e. cytology, biopsy or immunohistochemistry) and serological and molecular techniques (Solano-Gallego *et al.*, 2009; Elmahallawy *et al.*, 2014).

Prevention of Infection in Man and Animals

Control measures for man and dogs are available and include medical treatment, individual use of

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sand fly repellents in dogs, canine vaccines and immunomodulating drugs (Otranto and Dantas-Torres, 2013; Wylie *et al.*, 2014a,b).

Treatment for people and dogs in Europe is different, thus limiting the likelihood of developing resistance. People are commonly treated with a short course of amphotericin B (Murray *et al.*, 2005), while moderately to severely sick dogs are usually treated with a combination of a 1-month course of meglumine antimoniate or miltefosine and a long-term course of allopurinol. Generally, treatment in dogs leads to a clinical cure and decreased parasite load. However, complete parasitological cure in the majority of dogs appears to be unlikely (Solano-Gallego *et al.*, 2009).

Gaps in Knowledge and Recommendations for Further Research

There are numerous gaps in knowledge regarding *Leishmania* infection. These include: (1) a better understanding of the immunopathogenesis of the disease in man and dogs and how clinical disease appears versus subclinical infection, (2) knowledge of the immune mechanisms that control infection and how to develop efficacious vaccines for man and dogs, (3) understanding the role of domestic or wild mammals other than the dog as reservoirs of *L. infantum* infection and (4) understanding the risk factors associated with human and animal infection in Europe.

Giardiosis

Aetiology

The genus *Giardia* (Diplomonadida, Hexamitidae) includes intestinal protozoan parasites that infect numerous hosts, ranging from mammals to amphibians and birds. Currently, six *Giardia* species are accepted: *Giardia agilis*, *Giardia ardeae*, *Giardia muris*, *Giardia microti* and *Giardia psittaci* infecting various species of animals, while *Giardia duodenalis* infects man and many other mammals. *Giardia* species differ significantly in host range, with *G. duodenalis* (syn. *Giardia lamblia* and *Giardia intestinalis*) having the broadest host range and greatest public health significance (Feng and Xiao, 2011).

Although *G. duodenalis* is found in man and other mammals, including pets and livestock, it is now considered a multispecies complex. Historically, allozyme analyses placed all isolates from man into two genetic assemblages (assemblages A and B). Multigenic sequence analyses confirmed this assemblage separation and identified additional lineages of *G. duodenalis* from animals including assemblages A and B in man and other animals, assemblages C and D from dogs, assemblage E from artiodactyls, assemblage F from cats and assemblage G from rodents (Caccio *et al.*, 2005; Thompson *et al.*, 2008; Tysnes *et al.*, 2014).

Hosts and Life Cycle

Giardia is a very common enteric protozoal parasite of domestic animals, including livestock, dogs, cats and wildlife. *G. duodenalis* causes giardiosis in man and in most mammals. The life cycle of *Giardia* is direct and the infective stage of the parasite, the cyst, is immediately infectious when released into the faeces. Cysts remain infectious for months in cool, damp areas and accumulate in the environment. When ingested by the host, cysts excyst in the duodenum, releasing the trophozoites. The latter undergo repeated mitotic division in the gut lumen and form environmentally resistant cysts. Cysts pass through the intestine in faeces and are spread by contaminated water, food and fomites and by direct physical contact (Feng and Xiao, 2011).

Epidemiology

It has been estimated that about 200 million people in Asia, Africa and Latin America have symptomatic infection with *Giardia* (Feng and Xiao, 2011). Once infected, *Giardia* causes a generally self-limited clinical illness characterized by diarrhoea, abdominal cramps, bloating, weight loss and malabsorption. However, asymptomatic giardiosis occurs frequently, especially in developing countries. In Germany, on average, 3,806 notified giardiosis cases (range 3,101−4,626) were reported between 2001 and 2007, which corresponded to an average incidence of 4.6 cases/100,000 population (Sagebiel *et al.*, 2009). Much higher incidence rates were reported for some other countries. In the Netherlands, there were 11,600 cases in 2004, corresponding to 69.9 cases/100,000 population (Vijgen *et al.*, 2007).

The relationship between human and animal *Giardia* infection is not clear. Although people share the same *G. duodenalis* assemblages with animals with which they have close contact, such as household dogs, it is not known how frequently infection is actually acquired from household animal contact or whether both people and pets acquire it from a common source, such as contaminated water. Undoubtedly, people also commonly infect each other.

Infection rates with *Giardia* in dogs were 24.8% in a large study in Europe (Epe *et al.*, 2010), 22.7% in Belgium (Claerebout *et al.*, 2009) and 21.0% in the UK (Upjohn *et al.*, 2010). Infection rates in cats were 20.3% in a multicountry study in Europe (Epe *et al.*, 2010). Giardiosis in animals is often subclinical,

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but has been associated with the occurrence of diarrhoea and illness in puppies and kittens (Thompson, 2004).

Giardia infections are common in pigs, cattle, sheep, goats, elks and deer and other ruminants (Feng and Xiao, 2011). Although it is believed that infection with *Giardia* is associated with economic losses through the occurrence of diarrhoea, poor growth and even death in farm animals (Geurden *et al*., 2005), only a few studies have been conducted to assess the effect of giardiosis on livestock production or growth rates. In bottle-fed specific-pathogen-free lambs infected experimentally with *Giardia* cysts, infection was associated with delay in reaching slaughter weight and decreased carcass weight (O'Handley and Olson, 2006).

Diagnosis of Infection in Man and Animals

Giardia infection can be diagnosed by stool examination to identify cyst and trophozite stages in direct fresh stool smears or by flotation for cysts. Rapid detection of *Giardia* antigen can be made using immunochromatographic kits, by immunofluorescence, ELISA or PCR in a suitably equipped parasitology laboratory (Feng and Xiao, 2011).

Prevention of Infection in Man and Animals

The prevention of giardiosis in man is closely associated with the provision of clean fresh water and adequate sewage systems. Boiling or filtering water from the environment before drinking it is essential and removal of infected faeces from infected animals or people followed by proper disinfection is necessary. Adherence to personal hygiene habits such as washing hands and cleaning fresh food is important in limiting infection.

Gaps in Knowledge and Recommendations for Further Research

Gaps in knowledge of giardiosis include the need to clarify if there are animal reservoirs for human giardiosis and to what extent, if at all, human giardiosis can be caused by contamination from an animal source. In that respect, it would also be important to find out whether animals may be infected by their owners and suffer from clinical giardiosis. A vaccine for giardiosis would be beneficial for people and also for domestic animals.

Echinococcosis

Aetiology

The genus *Echinococcus* includes several species and genotypes of zoonotic cestodes (tapeworms). The adult stages occur in the intestines of canids and felids without clinical relevance. The larval stages develop in tissues of various organs of a variety of mammalian intermediate hosts, including man, as aberrant hosts. Cystic echinococcosis (CE) is caused by species of the *Echinococcus granulosus* sensu lato (s. l.) complex. In Europe, *E. granulosus* sensu stricto (s. s.) ('sheep strain') and *Echinococcus canadensis* (*Echinococcus intermedius*, 'pig strain') are of major zoonotic significance (Table 1). The controversially discussed taxonomy and the molecular epidemiology of the *E. granulosus* complex has been reviewed recently (Romig *et al*., 2015). Alveolar echinococcosis (AE) caused by *Echinococcus multilocularis* is one of the most pathogenic zoonoses in Europe and leads to death of people in 10–15 years if untreated (Eckert *et al*., 2011).

Hosts and Life Cycle

E. granulosus s.s. is mainly transmitted within a dog–sheep cycle in pastoral regions (Table 1);

Table 1
***Echinococcus* spp. in Europe and their definitive and intermediate hosts**

Echinococcus species	*Echinococcus strains or E. granulosus s. l. genotypes (G)*	*Definitive hosts*	*Intermediate hosts*	*Zoonotic significance*
E. granulosus sensu stricto (s. s.)	Sheep strain (G1, 2, 3)	Dog (fox*)	Sheep, cattle†, pig and other herbivores†	+ + +
E. ortleppi	Cattle strain (G5)	Dog	Cattle	+
E. canadensis	Cervid strain (G8, 10)	Wolf (dog)	Cervids	+
E. canadensis, (proposed *E. intermedius*)	Pig strain (G7)	Dog (wolf)	Pig, other herbivores†	+ +
E. equinus	Horse strain (G4)	Dog	Equids	–
E. multilocularis	European strain	Fox, dog, raccoon dog, (cat*)	Arvicolids and other rodents	+ + +

Zoonotic significance is graded as: –, none; +, mild; + +, moderate; or + + +, marked.
*Mostly low worm numbers with very low egg production.
†Mostly with strongly reduced protoscolex formation in the cysts often resulting in infertile cysts.

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however, other potential intermediate hosts can be involved. Interestingly, the development of protoscoleces in the cysts can be markedly reduced in cattle as compared with sheep. The *E. canadensis* (pig strain, G 7) cycle is characterized in the Baltic states and Poland by a small scale transmission pattern between farm dogs and pigs in family farms with the practice of traditional home slaughter (Bruzinskaite *et al.*, 2009), but possible wild or semi-wild animal cycles have been observed, including wolves in Portugal or wild boars in Corsica (Umhang *et al.*, 2014). *Echinococcus ortleppi* was prevalent in cattle all over central Europe, but has nearly disappeared without specific control programmes.

E. multilocularis is perpetuated in a wildlife cycle mainly by foxes as definitive hosts and small mammals as intermediate hosts. Definitive hosts with high reproductive potential of *E. multilocularis* are predominantly the red fox, the raccoon dog, the wolf and the domestic dog. After a prepatency of around 1 month, eggs are shed over a few months, but 95% of the total egg excretion occurs within the first month of patency (Kapel *et al.*, 2006). Wild felines and domestic cats have occasionally been found to harbour intestinal stages. Although cats are more likely to be infected with *E. multilocularis* than dogs, their zoonotic significance is estimated to be small, based on the low level of egg excretion. Dogs, on the other hand, may play a very important role in the transmission to man, but they probably do not contribute significantly to the contamination of rodent habitats as compared with foxes (Deplazes *et al.*, 2011; Hegglin and Deplazes, 2013).

Echinococcosis is not a food-borne zoonosis in the classical sense. Eggs are typically excreted fully developed and infectious (containing an oncosphere larva) by defecation in the environment. In addition, these eggs are highly resistant: *E. multilocularis* eggs survive in the environment for up to 8 months; however, they are sensitive to desiccation. Eggs can be dispersed from the deposition sites either by being washed away or carried by flies and other vectors (Eckert *et al.*, 2011). *Echinococcus* eggs may also adhere to tyres, shoes or animal paws, resulting in more widespread dispersal and contamination of the environment, including human dwellings.

Epidemiology

In Europe, the endemic area of *E. granulosus* s. s. covers southern and south-eastern Europe; *E. canadensis* G7 is prevalent in the Baltic countries, Poland and southwards to Romania. For *E. granulosus* s. l., most prevalence data are based on slaughterhouse investigations of intermediate hosts, while prevalence data concerning definitive hosts are scarce, especially for pet dogs. Prevalence rates of 0–31% are reported from farm and shepherd dogs in Italy and Spain and 14.2% from farm village dogs in Lithuania (Bruzinskaite *et al.*, 2009; Carmena and Cardona, 2013).

E. multilocularis occurs in the northern hemisphere, with large endemic areas in Europe including parts of the western continent (e.g. France, Benelux States) and all countries of central Europe including Northern Italy, Slovenia, Romania and the Baltic States. Furthermore, foci also exist in Denmark, Sweden and on Svalbard Island (Gottstein *et al.*, 2015) (Fig. 1).

Based on recently improved diagnostic strategies, several studies have investigated the prevalence of *E. multilocularis* in pet dog populations. Low prevalence rates of <0.5% were recorded in the privately owned dog populations in France, Germany, Switzerland and Denmark, but a higher prevalence (3–8%) was found in dogs with predatory habits and those able to roam more widely (Deplazes *et al.*, 2011). In Switzerland, 0.3% of randomly selected privately owned dogs were found to be infected with this tapeworm. Based on this prevalence, the individual probability of being infected at least once during 10 years can be estimated at 8.7%. Large population studies in Germany revealed that 0.13% of dogs in northern and 0.35% in southern Germany excreted *E. multilocularis* eggs in their faeces. Considering the total dog population in Germany (approximately 5.4×10^6 dogs), around 13,000 are estimated to be infected.

The prevalence of *E. multilocularis* in cat populations, as determined at necropsy examination, ranged between 0% and 5.5% in various endemic areas. Cat infections are characterized by low worm burdens and strongly reduced worm development, resulting in lower egg production compared with foxes or dogs. Therefore, the epidemiological role of the cat in spreading this infection is estimated to be low (Hegglin and Deplazes, 2013).

In the human population, CE is one of the five most frequently diagnosed zoonoses in the Mediterranean region and is re-emerging in South Eastern Europe (Jenkins *et al.*, 2005). Incidence rates for CE of 1.1–3.3/100,000 were recorded in Spain, up to 3.5 in Sardinia in Italy and 3.3 in Greece, Bulgaria and Romania (Torgerson *et al.*, 2011). Economic loss attributable to human CE was estimated for Spain at €133 million (Benner *et al.*, 2010).

Human AE is one of the most pathogenic helminthic zoonoses and causes a high burden of disease in Europe (Torgerson *et al.*, 2008). Recent studies support the hypothesis that the infection pressure caused

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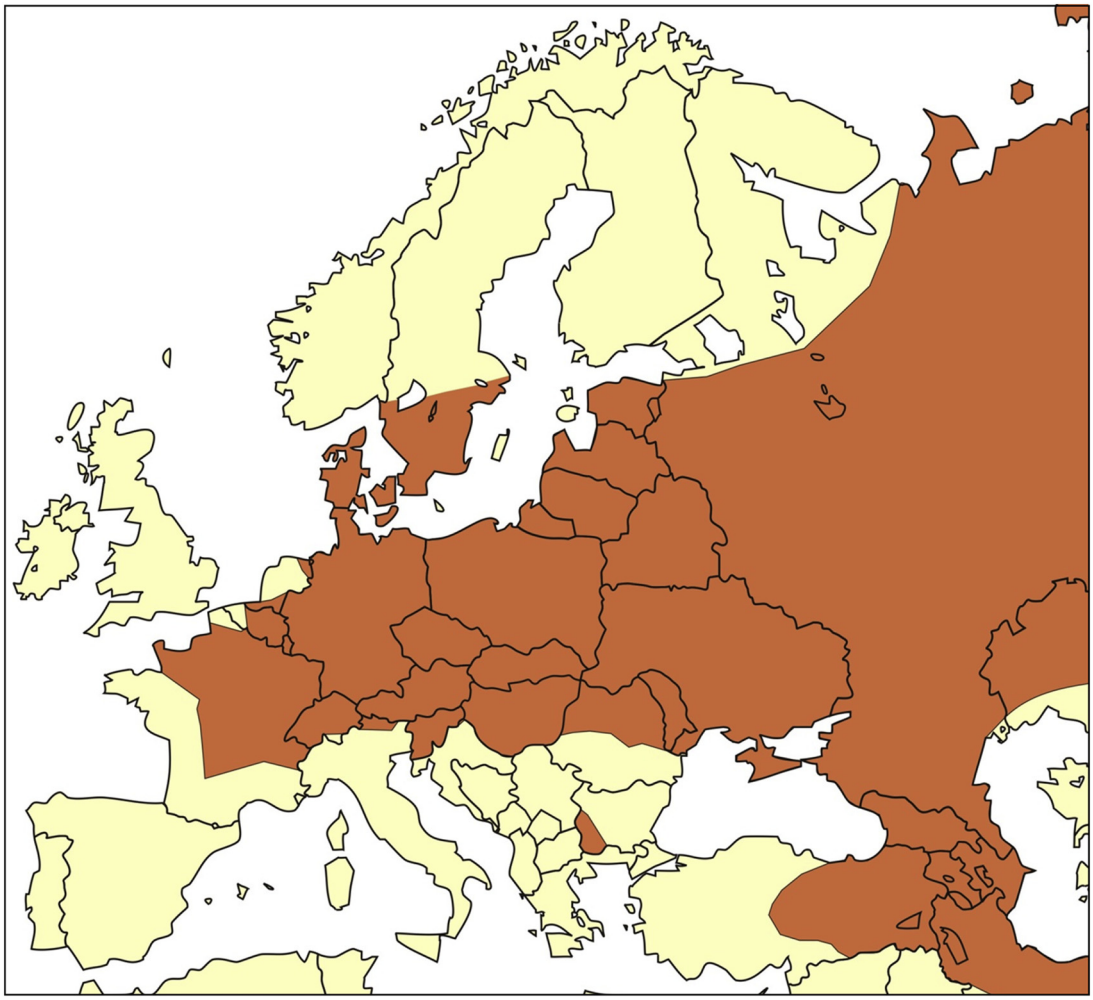

Fig. 1. Approximate distribution of *Echinococcus multilocularis* in Europe shown in dark orange colour (with permission from the Institute of Parasitology, University of Zurich, Switzerland).

by *E. multilocularis* eggs has increased across certain large European regions. In Switzerland, a representative endemic area for central Europe, the annual incidence rates of new human AE cases varied between 0.10 and 0.16/100,000 individuals over a 45-year period, suggesting a high degree of epidemiological stability. However, approximately 10–15 years (corresponding to the incubation time of AE) after a distinct increase in the fox populations (with *E. multilocularis* prevalences of 30–60%), a higher incidence rate of 0.25/100,000 was recorded (Deplazes *et al.*, 2011). Similar trends of increasing incidence have been observed in Austria, France and Lithuania. The overall incidence of AE is variable (0.03–0.26) in Central Europe, but estimated to be 200 new cases per year (Deplazes, personal communication).

Humans are exposed to eggs of *Echinococcus* spp. via different ways. The most important sources of infection are handling of definitive hosts and oral uptake of contaminated water, food or soil. Adherent eggs and even proglottids of *Echinococcus* have been observed on infected dogs in individual cases. Direct exposure to these eggs is influenced by occupation and behaviour, especially a close human–animal bond.

Domestic transmission of *E. granulosus* eggs from pet, stray and working dogs is particularly important in areas with inadequate educational standards and veterinary control. Risk factors for infection of intermediate and definitive animal hosts with *E. granulosus* s. l. have been recently reviewed (Otero-Abad and Torgerson, 2013; Craig *et al.*, 2015). Indeed, the number of owned dogs and the frequency of contact with dogs were identified as risk factors for human AE in studies from China (Craig *et al.*, 2015), while in a Spanish study, cohabitation with dogs and feeding of uncooked viscera were defined as risk factors for CE (Campos-Bueno *et al.*, 2000). As home

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slaughter of sheep in parts of Southern Europe and of pigs in parts of Poland and the Baltic states is still widespread, local family dogs may be infected by feeding of infected offal.

Diagnosis of Infection in Animals

Intestinal infections with *E. granulosus* or *E. multilocularis* are typically subclinical in definitive hosts. The diagnosis of the infection in dogs or cats has been considerably improved in recent years by egg isolation methods, coproantigen ELISAs and PCR tests for *E. granulosus* s. l. and for *E. multilocularis* (Craig *et al.*, 2015; Conraths and Deplazes, 2015). These techniques can also be used for the examination of faecal samples collected in the environment.

Prevention of Infection in Man and Animals

Comprehensive control programmes have so far only been applied for CE, with varying degrees of success (Craig and Larrieu, 2006) including control of stray dogs, slaughter supervision and public education campaigns, routine anthelmintic treatment of dogs and vaccination of sheep. More detailed control options for CE have been reviewed by Lightowlers (2013) and Barnes *et al.* (2012).

A treatment schedule individually designed for pets based on infection risks (e.g. free roaming, uncontrolled access to rodents or offal) can improve treatment efficiency against cestodes. Uniform guidelines for the control and treatment of parasites in pet animals were developed and published by the European Scientific Council on Companion Animal Parasites (ESCCAP) in Europe (www.esccap.org). The current recommendation is to treat dogs with access to *Echinococcus* metacestodes monthly with praziquantel in order to reduce environmental contamination with eggs. However, even strict compliance of the pet owners will not reduce the environmental contamination with eggs of *E. granulosus* caused by stray dogs or of *E. multilocularis* caused by foxes. The growing fox populations in Central Europe, especially in urban areas, with a prevalence of *E. multilocularis* infection above 30% is causing a high infection pressure and maintaining the parasite cycle without the pet population. Therefore, a promising approach is to reduce the infection pressure by the delivery of anthelmintic baits for foxes (Hegglin and Deplazes, 2013).

To prevent the introduction of *E. multilocularis* into Great Britain, Ireland and as of yet non-endemic Scandinavian countries, where, due to the presence of suitable intermediate hosts, the establishment of the parasite would be possible, the Pet Travel Scheme prescribed strict deworming regime of all dogs entering these countries.

Gaps in Knowledge and Recommendations for Further Research

Recommendations for further research and actions against echinococcosis include: (1) establishment of a One Health concept for systematic, specific and standardized surveillance of AE and CE in man and of *Echinococcus* infection in animals, (2) definition of minimal standards and harmonized approaches for the monitoring of the epidemiological state of these infections in Europe and (3) further development of control strategies adapted to the local and socio-cultural epidemiological situation to prevent both AE and CE in man.

Vector-borne Helminths

Aetiology

Filaroids are roundworms that belong to the family Onchocercidae. Filaroid species are prevalent in Europe and some of them are of increasing concern due to the significant level of disease they cause in dogs and man (Genchi *et al.*, 2011; Otranto and Eberhard, 2011; Morchón *et al.*, 2012). The species *Dirofilaria immitis* and *Dirofilaria repens* (Spirurida, Onchocercidae) are the best known filaroids affecting dogs. They present different pathogenic potentials for man and animals; while *D. immitis* threatens dogs and cats, causing a severe and often fatal cardiocirculatory disease referred to as 'heartworm disease', *D. repens* induces a non-pathogenic subcutaneous infestation in dogs, but is a more prevalent zoonotic pathogen in man (Dantas-Torres and Otranto, 2013). Mosquitoes transmit these *Dirofilaria* species to dogs, cats and other wild carnivores. About 45% of the total human and pet population are exposed to the risk of vector-borne helminths (VBHs) in Europe (Petrić *et al.*, 2012). Although *Dirofilaria* spp. represent the most prevalent VBHs, other helminths of dogs and cats, such as the *Thelazia callipaeda* eyeworm (Spirurida, Thelaziidae), are emergent zoonotic agents in several European regions (Otranto *et al.*, 2013a). Finally, the recent finding of the zoonotic potential of a little known filaroid of dogs, *Onchocerca lupi* (Spirurida, Onchocercidae), rendered the puzzle of human VBH infections in Europe even more complicated.

Hosts and Life Cycle

Dirofilarioses are transmitted by bloodsucking mosquitoes, primarily to dogs, although cases of infection in man are reported increasingly (Otranto and Eberhard, 2011). Soon after mosquitoes inoculate

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infective third-stage larvae (L3) to dogs and cats, developing larvae migrate to the definitive site of parasitism, the pulmonary arteries and right chambers of the heart for *D. immitis* and the subcutaneous tissues for *D. repens*. In these locations, following their development into adult worms (in 120–180 and 189–259 days for *D. immitis* and *D. repens*, respectively), females release microfilariae into the blood of the definitive host (Genchi *et al.*, 2009), which are thereafter ingested by mosquitoes during their blood intake. Microfilariae of *Dirofilaria* spp. develop in the intermediate mosquito vectors from embryos to infective L3 larvae in a variable period of time at a minimum threshold of 14°C and the requirement of a minimum of 130 days for larvae to reach infectivity (Genchi *et al.*, 2009).

T. callipaeda nematodes live in the orbital cavities and associated host tissues, causing ocular disease in carnivores and representing a potential public health concern due to the zoonotic impact. Adults live in the conjunctival sacs of animals under the nictitating membrane and the mature females release first-stage larvae (L1) into the lachrymal secretions, which are ingested subsequently by the zoophilic fruit fly *Phortica variegate* (Diptera, Drosophilidae), the known vector of this spirurid in Europe (Otranto *et al.*, 2005). In the intermediate host, L1s undergo development to L3s approximately 14–21 days after infestation (in laboratory conditions) and may also survive in overwintering flies for 6 months (Otranto *et al.*, 2004, 2005). Finally, mature L3s migrate through the arthropod coeloma to the labella to be then transmitted to a receptive host as soon as the drosophilid feeds on the lachrymal secretions (Otranto *et al.*, 2005).

Scant information is available on *O. lupi*, which localizes in nodular lesions under the sclera and periocular tissues of dogs and cats or in the retrobulbar eye (Otranto *et al.*, 2013b). The biology of this filaroid in the definitive host is almost unknown and the vector of this infestation is not well characterized (Otranto *et al.*, 2012a).

Epidemiology

The interaction between helminths, vectors and animals is the consequence of a complex range of biological (e.g. vectorial capacity, biting rates) and environmental (e.g. climate, population movements and trade) factors, which ultimately affect the epidemiology of VBH infections. This picture is complicated further by the fact that new potential vectors are introduced into previously non-endemic areas, therefore increasing the risk for establishing new transmission cycles in populations of susceptible hosts. This was the case for the introduction of the invasive mosquito species *Stegomyia albopicta* (*Aedes albopictus*) into Italy (Romi and Majori, 2008), which most likely contributed to the spread of *D. immitis* from endemic areas of the Po river valley in northern Italy to southern Italy (Otranto *et al.*, 2009). However, several mosquito species of the genus *Anopheles*, *Aedimorphus*, *Armigeres*, *Ochlerotatus*, *Stegomyia*, *Culex*, *Coquillettidia* and *Mansonia* may act as intermediate hosts, although *Aedimorphus vexans* (*Aedes vexans*), *Culex pipiens pipiens* and *S. albopicta* are also implicated as the most important natural vectors of these worms in Europe. Since both *D. repens* and *D. immitis* grow under laboratory conditions in the same mosquito species with similar developmental times, these infections are often sympatric in animal populations (Genchi *et al.*, 2009). The relationship between the prevalence of *D. repens* in dogs and the occurrence of human cases of dirofilariosis, based on a review of the historical literature, was evident in some provinces of Sicily (Otranto *et al.*, 2011a). Indeed, while *D. immitis* is recognized as the main agent of human dirofilariosis in the Americas and was described in a few cases in Italy, Greece and Spain (Miliaras *et al.*, 2010; Morchón *et al.*, 2010; Avellis *et al.*, 2011), *D. repens* is the most prevalent species infesting people in Europe (Pampiglione *et al.*, 1995, 2009). Human cases of dirofilariosis are increasing in Europe, most likely paralleling the spreading of infection in dogs in central and north-eastern European countries including Poland, Switzerland, the Czech Republic, Hungary, Romania, Serbia and the Slovak Republic (Genchi *et al.*, 2014) (Fig. 2).

Over the last 20 years, *T. callipaeda* has been repeatedly reported to infest the eyes of domestic (dogs and cats) and wild carnivores (foxes, wolves, beech martens and wild cats). Countries considered as endemic for this worm in Europe include Italy, France, Switzerland, Spain and Portugal (Malacrida *et al.*, 2008; Miró *et al.*, 2011; Vieira *et al.*, 2012; Otranto *et al.*, 2013b). The same areas where the infection was recently diagnosed were predicted by a model published about 10 years before, which was based on the ecology and the seasonal occurrence of the drosophilid fly in a highly endemic area of southern Italy (Otranto *et al.*, 2006). Indeed, that model anticipated that large areas of Europe were likely to represent suitable habitats for *Phortica variegata* and, therefore, for the expansion of thelaziosis. Consequently, the first cases of human thelaziosis in Europe have been diagnosed in north-western Italy, south-eastern France (Otranto and Dutto, 2008) and Spain (Fuentes *et al.*, 2012).

O. lupi has been found to infect dogs in southern (Greece, Portugal) and Central Europe (Germany,

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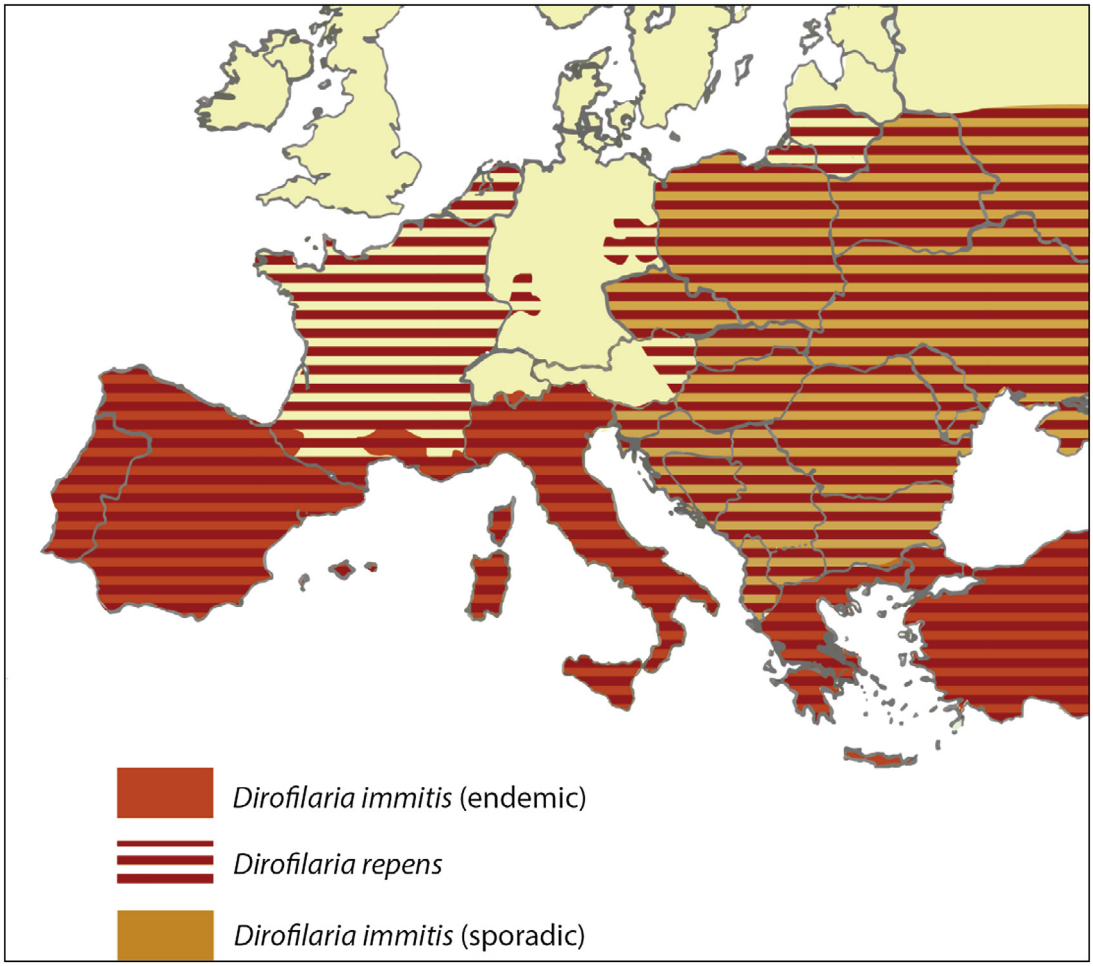

Fig. 2. Distributions of *Dirofilaria immitis* and *Dirofilaria repens* infections in Europe (with permission from the Institute of Parasitology, University of Zurich, Switzerland).

Hungary and Switzerland) (Széll *et al.*, 2001; Komnenou *et al.*, 2002; Hermosilla *et al.*, 2005; Faísca *et al.*, 2010; Otranto *et al.*, 2013a) and in the USA (Orihel *et al.*, 1991; Eberhard *et al.*, 2000; Zarfoss *et al.*, 2005) where it was recently found also in cats (Labelle *et al.*, 2011). Since the first report of human ocular infestation (Otranto *et al.*, 2011b), *O. lupi* has been recognized as a zoonotic agent in patients from Turkey (Otranto *et al.*, 2012b; Ilhan *et al.*, 2013), Tunisia (Otranto *et al.*, 2012b), Iran (Mowlavi *et al.*, 2013) and the USA (Eberhard *et al.*, 2013).

Diagnosis of Infection in Man and Animals

Diagnosis of VBH infections is achieved through detection of circulating microfilariae (e.g. *D. immitis* and *D. repens*) in the bloodstream of infected animals by microscopical techniques, with the Knott's method as the gold standard (McCall *et al.*, 2008). In contrast, dermal microfilariae of *O. lupi* can be detected in skin biopsy samples from the interscapular region and the head (Otranto *et al.*, 2013a). While the morphological discrimination of microfilariae might be challenging and lack in sensitivity, as other filaroids may infect dogs (e.g. *Acanthocheilonema reconditum*, *Acanthocheilonema dracunculoides*), an alternative method for diagnosing *D. immitis* infection in dogs is the use of commercial kits for the detection of antigens released into the blood by adult females. The acid phosphatase histochemical staining method can be useful for differentiating microfilariae of *D. immitis*, *D. repens* and *A. reconditum* based on species-typical staining patterns of their anatomical structures, although this method presents limitations for the identification of microfilariae and major disadvantages due to the short shelf-life of its reagents (Peribáñez *et al.*, 2001). Recent molecular-based assays have enabled identification of filaroids, irrespective of their life cycle stage (Latrofa *et al.*, 2012).

In man, *Dirofilaria* spp. localize predominantly in the subcutaneous tissues and lungs, but also in the

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central nervous system, causing a range of clinical manifestations ranging from asymptomatic infection to fatal syndromes (Otranto and Eberhard, 2011). Diagnosis in human patients is usually only possible after surgery and extraction of the worm from the tissues for *Dirofilaria* spp. and *O. lupi* and often requires the assistance of a specialist with an appreciation of the microscopical features of helminth histology (Otranto and Eberhard, 2011). Molecular characterization of samples also assists in achieving a diagnosis from the tissue biopsies.

Prevention of Infection in Man and Animals

The prevention and the treatment of VBH infections in endemic areas is challenging, due to the many components involved in the epidemiology and biology of these infections in man and animals. In dogs, dirofilariosis can be prevented with a number of macrocyclic lactones administered in different formulations (e.g. tablets, chewable, spot on and injectable) with different protocols, from daily administration up to slow release products with effects lasting for 6 months, which kill *D. immitis* or *D. repens* larvae before they develop into adults. The injectable long-lasting formulation containing moxidectin is effective in controlling *D. immitis* and *D. repens* infestations for a period of 6 months after a single administration (Genchi *et al.*, 2002, 2010). Current guidelines on management of *D. immitis* infection in dogs formed by ESCCAP and by the American Heartworm Society suggest extending preventive treatment to 7–8 months or even year round. No data are available on the efficacy of macrocyclic lactones as chemoprophylactic agents against *O. lupi*, while preventing contact with the fly intermediate host of *T. callipaeda* by use of bed nets is currently the only strategy to prevent this infection.

Gaps in Knowledge and Recommendations for Further Research

While the scientific knowledge of the biology, epidemiology, control and treatment of *D. immitis* and *D. repens* has increased considerably over past decades, for other filaroids such as *O. lupi* there are still gaps in knowledge that impair a realistic appreciation of their impact in veterinary and human medicine. In addition, the reasons why human cases of VBH infections have increased in Europe are not fully known, but this most likely reflects the spread of arthropod vector species and lack of economic means for their control in the environment. Large epidemiological studies to estimate the occurrence of filaroid infections in animals, coupled with entomological surveillance programmes, are essential for providing information on the occurrence of these pathogens and to prevent the spread of filaroids into non-endemic areas, therefore limiting the outbreaks of zoonotic filariosis.

Toxocariosis

Aetiology

Toxocariosis is caused by *Toxocara canis* and *Toxocara cati* (syn. *Toxocara mystax*), which are ubiquitous, prolific nematodes with a complicated life cycle. Other ascarids that may potentially be of clinical importance in man include *Baylisascaris procyonis* of raccoons and *Ascaris suum* of pigs. In contrast to the other nematodes, the latter is expected to complete its migration and may reach patency in man (Nejsum *et al.*, 2012).

Hosts and Life Cycle

The definitive host of *T. canis* are canids, including dogs and foxes, while *T. cati* has cats and other felids as definitive hosts. Invertebrates (e.g. earthworms), rodents, foxes, birds and livestock (e.g. sheep, pigs and poultry) can serve as paratenic hosts (Taira *et al.*, 2004; Schnieder *et al.*, 2011). Dogs are infected with *T. canis* by ingestion of embryonated eggs or hypobiotic (arrested) L3 in paratenic hosts; even older immune dogs may acquire new patent infections if exposed to low numbers of eggs (Fahrion *et al.*, 2008). Pups are infected vertically, either prenatally in the last trimester of gestation or by larvae in milk from the bitch. Transplacental transmission accounts for many more infections than the lactational route (Burke and Roberson, 1985) and represents either recent infection of the pregnant bitch or reactivated hypobiotic larvae after somatic migration in the immune bitch (Schnieder *et al.*, 2011). Occasionally, bitches are reinfected by eating intestinal larvae (L4) from faeces of pups. *T. cati* is primarily transmitted to kittens by ingestion of larvae in milk following acute infection of the queen, while prenatal infection apparently does not take place (Coati *et al.*, 2004). The lack of reactivation indicates different characteristics of hypobiotic larvae in cats compared with dogs. Other infection routes in cats are intake of embryonated eggs from soil or larvae within paratenic hosts (e.g. rodents).

The life cycle is typically migratory: after ingestion of eggs in a fully susceptible host, hatched larvae migrate through the liver and lungs while moulting from L3 to L4, are coughed up through the trachea (L4 to L5) to finally develop into adults that reside in the small intestine of the definitive hosts. Eventually, eggs in large number (thousands per day) are voided in the faeces. In the immune host, the larvae do not perform tracheal migration, but re-enter the

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circulation for somatic migration (i.e. L3 relocate to skeletal muscles, kidneys, mammary gland, CNS and other organs) (Schnieder *et al.*, 2011). For *T. canis*, the prepatent period thus varies with the route of infection; eggs can be found in puppies 2–3 weeks of age after prenatal infection, while prepatency is 4–5 weeks after ingestion of eggs followed by tracheal migration (Overgaauw, 1997). Eggs are usually excreted for 4 months. The prepatent period for *T. cati* is also variable, but is usually 6–8 weeks after ingestion of eggs. Patency lasts 4–6 months. Eggs undergo development outside the host for at least 2–4 weeks to reach the infective stage (L3), which remains inside the egg and shows extreme persistence in the environment for months to years, although it is generally sensitive to ultraviolet light, desiccation and high temperature.

Human infections are predominantly acquired from ingestion of embryonated eggs by geophagia in sandpits, parks or other places where cats, dogs or wildlife have defecated. *Toxocara* spp. eggs have been recovered worldwide from sand or soil in playgrounds and public parks (Overgaauw, 1997). Embryonated eggs have also been found in the hair coat of dogs, mainly puppies (Amaral *et al.*, 2010) and foxes, but the relative importance of this for human transmission remains unknown. Food-borne infections may also take place, for example by drinking water or eating vegetables contaminated with eggs and by eating raw liver or other viscera of paratenic hosts, including livestock, as experimentally demonstrated for pigs or chickens (Taira *et al.*, 2004). It is possible that food-borne infections may be relatively common in certain cultural settings, for instance in Japan where raw liver is eaten (Akao and Ohta, 2007), but the relative importance of this means of transmission in the European context is presently unknown.

Raccoons are the major definitive hosts of *B. procyonis*, but infection also reaches patency in dogs; the latter has been observed in many cases in the USA (Lee *et al.*, 2010), usually with low intensity infections. However, no data for dogs in Europe have been reported. A wide range of animals (>90 species of mammals and birds) may serve as intermediate hosts, as it is believed that the L2 stage is in the ingested infective egg and it develops to L3 in the intermediate host (Kazacos, 2001). In raccoons, there is no migration, while there is extensive somatic migration in the intermediate hosts. A proportion of larvae has propensity for migration in the CNS (neural larvae migrans, NLM). This is particularly harmful as development from L2 to L3 is accompanied by a four- to five-fold increase in length (up to 1,300–1,900 μm) and larvae do not readily encapsulate in eosinophilic granulomas as in other tissues, but continue migration for a prolonged period of time (Kazacos, 2001).

Epidemiology

The heaviest infections and highest morbidity are seen in pups and kittens. Heavy prenatal infections in pups may lead to severe disease with alternating diarrhoea and constipation, vomiting, typical 'pot belly', reduced growth with cachexia, poor hair coat and in some cases death (Schnieder *et al.*, 2011). Dogs older than 6 months are usually less severely or not affected. Clinical signs of *T. cati* infection in young cats are similar, but generally less severe; respiratory tract signs are also reported. The prevalence of *T. canis* in dogs, based on faecal examination, varies considerably in EU countries (1.4–30.5%) (Schnieder *et al.*, 2011) and depends on the composition of the host population, animal density (definitive and paratenic hosts), seasonality, region and methods employed. The prevalence of *T. cati* is generally higher due to the low level of resistance to reinfection in older cats, around 8–76% (Overgaauw, 1997), with large variation between domestic cats with or without access to the outdoors, stray cats or those in shelters. In foxes, *T. canis* has been reported with mean prevalence rates up to 49–87%, depending on age group (Saeed *et al.*, 2006; Morgan *et al.*, 2013). Similar infection levels of *B. procyonis* (39–80%) have been reported in raccoons in some areas of Germany (Bauer, 2011).

Seroprevalence of *Toxocara* spp. infections in man is around 3–19% in many European countries, varying by diagnostic methods, age profile (highest in young people) and cultural habits (Overgaauw and Knapen, 2013). A certain level of cross-reaction with other nematode infections cannot be ruled out; for example, *A. suum* from pigs may cause patent (or aborted) infections in man, particularly in young individuals (Nejsum *et al.*, 2012). Risk factors related to seropositivity include young age, playing in sandpits, dog ownership, poor sanitation, rural populations and low socioeconomic status, while the effect of gender is variable (Magnaval *et al.*, 2001; Rubinsky-Elefant *et al.*, 2010). The vast majority of human *Toxocara* spp. infections are asymptomatic. However, *T. canis* and, probably less commonly, *T. cati*, may cause clinical syndromes in man described as visceral larvae migrans (VLM), ocular larvae migrans (OLM), covert toxocariosis and more rarely NLM. VLM and OLM are most often observed in children (VLM at 1–5 years of age predominantly; OLM at 5–10 years), while the less well-defined covert toxocariosis is found in both children and adults (Smith *et al.*, 2009). The incidence in

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the EU is largely unknown, but presumably very low (Smith *et al.*, 2009), and the relative contribution of the two species is unknown (Fisher, 2003; Rubinsky-Elefant *et al.*, 2010). Signs of VLM depend on the infective dose and are non-specific, including abdominal pain, fever, anorexia, respiratory signs, headache, skin lesions and occasionally neurological symptoms, accompanied by hepatomegaly and eosinophilia. OLM indicates the location of a *Toxocara* larva in an eye or optic nerve and is often painless, but leads to visual disturbances and unilateral blindness. It is increasingly seen also in adults (Akao and Ohta, 2007). Specific antibody levels in OLM are often low because the larvae evade the immune system or their number is low. There are some indications that *T. canis* and *T. cati* larvae have different tissue preferences during somatic migration in the same paratenic host or at least different time courses (Strube *et al.*, 2013). *T. cati* larvae predominantly locate in skeletal muscles while *T. canis* more rapidly migrate to the CNS in addition to the muscle, indicating perhaps a higher degree of neuroaffinity.

B. procyonis eggs are particularly abundant in latrine areas of raccoons and people contract infection mainly by geophagia (Bauer, 2013). As mentioned, *B. procyonis* causes severe OLM and NLM (acute eosinophilic meningoencephalitis) in intermediate hosts, including man. The NLM syndrome is often fatal or causes permanent neurological disease to the intermediate host, as observed in almost all reported human cases in the USA (Lee *et al.*, 2010). Only single cases in people have been reported from Europe (Bauer, 2013).

Diagnosis of Infection in Man and Animals

Patent infections in dogs and cats can be diagnosed by standard faecal flotation. A study combining PCR analysis and egg morphology showed that *T. cati* eggs are distinctly smaller than *T. canis* eggs, but also revealed that up to 30% of eggs found in dogs could be *T. cati* (Fahrion *et al.*, 2011). This is most likely due to coprophagia, as these species seem to be host specific. Ingestion of fox faeces by dogs may also lead to false-positive observations. *B. procyonis* eggs can easily be mistaken for *T. canis* eggs based on size; however, the latter have a regular pitted surface while *B. procyonis* eggs have a fine granular surface (Kazacos, 2001; Lee *et al.*, 2010). This may, however, be difficult to ascertain by routine microscopy and baylisascariosis needs in most cases to be confirmed by PCR on eggs.

Human toxocariosis is diagnosed by clinical manifestations, ophthalmology (OLM), clinical pathology, including eosinophilia, bioimaging (typically in CNS involvement) and serology. In cases of OLM and perhaps NLM, extirpation by biopsy and subsequent histopathology can be performed and parasite material can be speciated by PCR. Detection of IgG antibodies to *T. canis* excretory/secretory antigens (TES) by indirect ELISA, followed by western blot to limit cross-reactivity, is central to the diagnosis (Fillaux and Magnaval, 2013). However, antibody titres do not necessarily correlate with active versus non-active infection and false-positive outcomes exist (Smith *et al.*, 2009). These assays cross-react with *T. cati* and can be used for evaluating toxocariosis as such; none of the currently available tests are capable of discriminating between *T. canis* and *T. cati* infections in man or any other paratenic host.

Prevention of Infection in Man and Animals

A cornerstone in prevention is minimizing the environmental contamination with (infective) eggs by rigorous removal of faeces and by treatment of infected dogs and cats. Faeces should be removed and destroyed when dropped in public areas, streets, kennels and also in private gardens. Intestinal stages of *Toxocara* spp. are susceptible to the most commonly used anthelmintics, while hypobiotic stages in tissues are impossible to treat effectively, thus posing a problem of clearing breeding bitches of infection (Othman, 2012). Although some hypobiotic larvae may become susceptible to anthelmintics on reactivation, it is not advisable to treat pregnant animals to reduce perinatal transmission (Overgaauw and Knapen, 2013). Repeated application of anthelmintics is therefore recommended for puppies and kittens (and their mothers) during lactation and early life in order to avoid pathogenic infections and limit contamination (Fisher *et al.*, 1993). Older dogs and cats can either be treated on a routine basis or examined for eggs regularly followed by treatment of patent cases. Guidelines for the control and treatment of parasites in pet animals were developed and published by ESCCAP in Europe (www.esccap.org). Other preventive measures include avoiding transmission by feeding of raw liver or offal and coprophagy in dogs. The relative contribution of *T. canis* from foxes to environmental contamination is difficult to assess in an urban context and equally difficult to control. An attempt to quantify the contributions of dogs, cats and foxes in the Bristol area (UK) indicated that the main contributor was dogs, although obviously modified by the degree of removal of faeces and dog access to public spaces (Morgan *et al.*, 2013).

Prevention of human infections should be based on appropriate control of infections in pets, removal of

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faeces from surroundings, limiting access of pets to children's play areas, good hygiene and lastly, education. The environmental efforts include fencing of playgrounds, covering of sandpits, regular application of new sand, exclusion of dogs from parks and recreational areas, provision of information (signs) and bags for faeces and management of stray animals. Furthermore, general good hand hygiene, rinsing of fresh produce from gardens and prevention of geophagia in children are essential.

Treatment of larvae migrans in people includes anti-inflammatory and anthelmintic treatments with moderate reduction in clinical symptoms (Strube *et al*., 2013) and in the case of OLM, possible extirpation. Anthelmintics may have limited effect in OLM.

B. procyonis infections in dogs are treated with commonly available anthelmintics, such as benzimidazoles, macrocyclic lactones or tetrahydropyrimidines. Raccoon populations should be controlled as well as any animal considered infected. Latrines close to children's playgrounds should be cleaned by disposal of faeces and preferably by burning (or removal) of the upper soil layer (more info on http://www.cdc.gov). Raccoons kept as pets or in contact with the public should be treated regularly.

Gaps in Knowledge and Recommendations for Further Research

Gaps in knowledge that need to be addressed include: (1) evaluation of the importance of food-borne transmission, in comparison with other transmission routes; (2) standardization of case definitions for human infection throughout Europe, which will enable the gathering of good quality data on the incidence and prevalence of disease; (3) evaluation of burden of disease in man, including the potential impact of subclinical infections on human behaviour; (4) development of diagnostic methods to discriminate between *T. canis* and *T. cati* in paratenic hosts, including man. This will provide information on infection routes and assist in better targeting of control strategies; (5) quantifying the animal sources of *Toxocara* environmental contamination (dogs, foxes or cats); (6) development of rapid point-of-care diagnostic tools for *Toxocara* in pets (e.g. coproassays for antigen or DNA). At present, most infections will remain unnoticed by companion animal owners and veterinarians unless faecal evaluation is performed; and (7) development of specific rapid detection for *B. procyonis* infections in dogs, which is important as the eggs look like *Toxocara* eggs and at present, a subsequent PCR on isolated eggs is most often needed to verify the diagnosis.

Conclusions

Parasitic zoonoses constitute some of the most important and common infections threatening human populations in Europe as well as other continents. This review has presented the major diseases in this category associated with companion animals, describing the current status of infections in man and animals in an effort to highlight gaps in knowledge and potential interventions to prevent or limit their spread. Combating parasitic zoonoses requires an integrated multidisciplinary approach involving collaboration between veterinary and medical scientists and policy makers.

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Conflict of Interest Statement

The authors declare that they have no competing interests.

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